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Synthesis of 6,6′-ether linked disaccharides from D-allose, D-galactose, D-glucose and D-mannose; evidence on the structure of coyolosa

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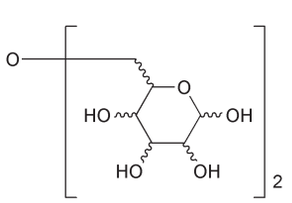
6,6′-Linked ethers derived from D-allose, D-galactose, D-glucose, and D-mannose have been prepared in order to allow comparisons with the reported 6,6′-linked hexopyranose coyolosa, an hypoglycemic compound which has been isolated by extraction of the root of the palm *Acrocomia mexicana*. Comparison of NMR data from the ethers and their derived peracetates with corresponding reported data from coyolosa and its peracetate indicate that coyolosa is not a 6,6′-linked disaccharide. The synthesised compounds are representatives of a novel class of disaccharide derivatives which are linked *tail to tail* in contrast to the more usual *head to tail* (*e.g.* maltose) or *head to head* (*e.g.* trehalose) disaccharides.

Introduction

In 1992, Pérez and co-workers reported[1] that the methanol extract of the charred root of the thorny palm *Acrocomia mexicana* exhibited hypoglycemic activity on normal and alloxan-diabetic rats. The charred root of this palm was reported to have been used in Mexico in traditional medicine for many years. In 1997, by column chromatography of the methanol extract, the research group isolated[2] from the most pharmacologically active fractions a crystalline solid, mp 170–172 °C, which they named coyolosa. On the basis of elemental analysis and that of its peracetate and also on NMR spectroscopic and mass spectrometric data, the authors proposed a structure for coyolosa as a 6,6′-ether linked disaccharide, an unusual *tail-tail* type structure in view of the paucity of examples in Nature of carbohydrates joined by ether links rather than by the more usual *head-head* (*e.g.* trehalose) or *head-tail* (*e.g.* maltose) linkages. In an attempt to provide evidence to identify coyolosa unequivocally, we synthesised[3] the 6,6′-linked D-allose derivative, since the formula presented by Pérez and co-workers[2] indicated *allo*-stereochemistry albeit, perhaps unintentionally, with the two moieties being D- and L-forms, but the physical properties of the synthetic material and its peracetate did not agree with those reported for coyolosa. Further, Ikegami and co-workers very recently reported a novel synthetic route to several 6,6′-ether linked disaccharides[4] and on the basis of structure–activity relationships they proposed that coyolosa may be the 6,6′-ether linked D-mannose derivative. We now give full synthetic details in support of our earlier preliminary publication regarding the D-allose derived pseudo disaccharide and describe the subsequent preparation and properties of the 6,6′-ether linked derivatives of D-galactose, D-glucose, and D-mannose.



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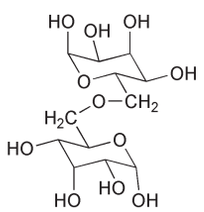

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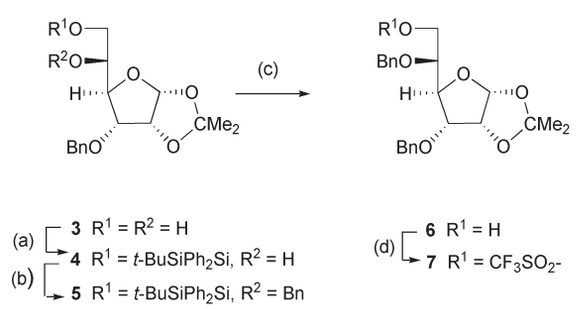

Scheme 1 *Reagents and conditions*: (a) *t*-$BuSiPh_2Cl/C_5H_5N$, 94%. (b) $NaH/PhCH_2Br/DME$, 68%. (c) Bu_4NF/THF, 91%. (d) $Tf_2O/Et_3N/CH_2Cl_2$, 80%.

Results and discussion

Selective protection of the primary hydroxy group in 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-allofuranose[5] **3** (Scheme 1) by reaction with *tert*-butyldiphenylsilyl chloride afforded **4** which on benzylation gave the fully protected allofuranose derivative **5**. De-*O*-silylation was achieved in good yield on treatment with fluoride ion to give the key intermediate **6**, from which the corresponding triflate **7** was prepared. In view of the relative instability of triflates in general, the sulfonate was purified by rapid passage through a column of silica, giving material homogeneous by TLC, and this was then used immediately. Reaction of the pre-formed sodium alkoxide derived from alcohol **6** with a slight excess of triflate **7** (Scheme 2) led to almost complete conversion to a new product in high yield, the 6,6′-linked compound **8**. The superiority of triflates in this type of S_N2 reaction is noteworthy; Ikegami and co-workers reported[4] that their attempts to forge a 6,6′-link in a similar type of reaction in the D-glucopyranose series using the reaction of the 6-alkoxide with a 6-iodide or a 6-tosylate gave only low to moderate yields and led them to develop an alternative synthetic strategy.

Catalytic hydrogenolysis of **8** to give **9** followed by de-*O*-acetalation afforded 6-*O*-(6-deoxy-D-allos-6-yl)-D-allose **10** as a hygroscopic solid. NMR spectroscopy in D_2O indicated that in this solution the β,β-pyranose form (δ_H 4.88, $J_{1,2}$ 8.2, 1-H) was predominant to an extent of ~81%, with a minor amount (~13% of the total anomeric signal) for an α-anomeric form (δ_H 5.13, $J_{1,2}$ 3.4, 1-H). Clearly, in this and other cases, the α-anomeric moiety could be associated with a β-pyranose moiety, since it is most likely that the two linked pyranose rings give rise to signals in the NMR spectrum independently of each other. Two small signals (6% of total) were observed at δ_H 5.23 and 5.36, and presumably represented furanose forms. The proportions of the anomers agree well with those reported[6] for D-allose aqueous solution of 77.5% β-pyranose, 14% α-pyranose, and 8.5% furanose forms. In its ^{13}C NMR spectrum in D_2O, compound **10** showed signals for anomeric carbons at δ_C 94.19 (major) and 93.57 (minor) which are in close agreement with those for β- and α-D-allose at 94.3 and 93.7, respectively[7] and

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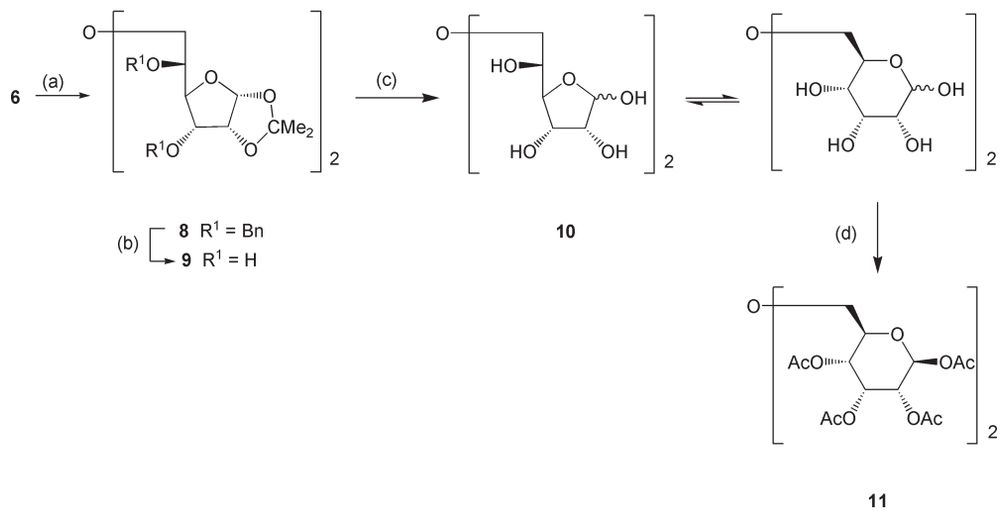


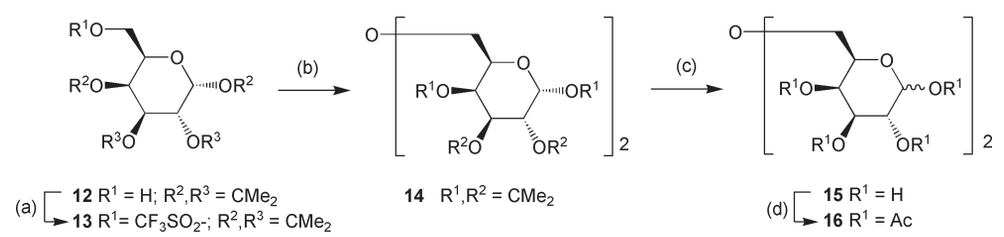
Scheme 2 *Reagents and conditions*: (a) NaH/THF then **7**, 89%. (b) H_2/Pd–C/EtOH–EtOAc, 85%. (c) CF_3CO_2H/H_2O (9 : 1), 96%. (d) Ac_2O/C_5H_5N, 62%.

there was a characteristic shift in δ_C of 6-C compared to that in the monosaccharide of 9.2 ppm to lower field. Acetylation of **10** with acetic anhydride in pyridine gave a crystalline octaacetate **11** with the β,β-configuration at the anomeric centres (δ_H 5.97, $J_{1,2}$ 8.7, 1-H and δ_C 90.06, 1-C) but its mp (198–199 °C) is considerably higher than that (132–134 °C) reported for the peracetate of coyolosa prepared by the same method. This discrepancy together with other NMR spectroscopic data (see later) indicates that coyolosa is not the *allo*-isomer in this type of compound.

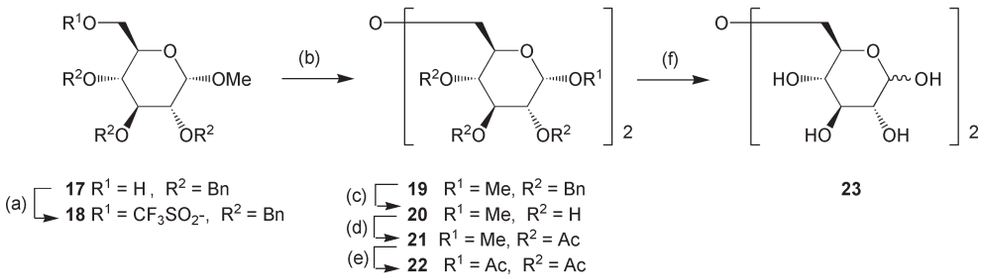
One of the few reports of a 6,6′-ether linked disaccharide prior to the present studies[3,4] is a patent[8] (on which the author has been unable to obtain any further details) on the preparation of such a derivative from 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose[9] **12**. In our study, triflate **13**, prepared in the usual manner by reaction of **12** with triflic anhydride using pyridine as the base, was reacted in THF solution with the sodium alkoxide of **12** to afford the 6,6′-ether **14** in good yield (Scheme 3). In investigating an alternative route, a solution of the alcohol **12** and triflate **13** in 1,2-dichloroethane was stirred under reflux in the presence of anhydrous potassium carbonate for 10 days, which led to the gradual formation of the same product **14**, although starting alcohol **12** and, surprisingly, the triflate **13** were still present in the reaction mixture even after this extended reaction time. Acidic hydrolysis of the ether **14** gave 6-*O*-(6-deoxy-α,β-D-galactopyranos-6-yl)-α,β-D-galactopyranose **15**. The NMR spectra of **15** in D_2O clearly indicated the presence of α- and β-pyranose rings in an α/β ratio of 0.59 with signals for 1-H at δ_H 5.25 ($J_{1,2}$ 3.7) and δ_H 4.57 ($J_{1,2}$ 7.8), data which compare well with those reported[10] for α- and β-D-galactose at δ_H 5.16 ($J_{1,2}$ 3.8) and δ_H 4.48 ($J_{1,2}$ 8), respectively, and an α/β ratio[6] of 0.47. The presence of the two anomeric forms was confirmed by the ^{13}C spectrum which had signals at δ_C 97.14 (major) and 93.05 (minor), in good agreement with those reported[7] for the monosaccharide. Three closely spaced peaks for 6-C were apparent at δ_C 71.14, 71.29 (major) and 71.41, which may be attributed to 6-C nuclei in the α,α- (or α,β-), β,β-, and α,β- (or α,α-) isomers, respectively. The region of absorption for the 6-C nuclei in **15** showed the characteristic shift to low field with respect to that of the anomers of D-galactose.[7]

Acetylation of **15** gave octaacetate **16** as a mixture of anomers as evidenced by the complexity of the ^1H spectrum which showed, apart from the broad singlet for 1-H in the α-anomer at δ_H 6.27, two signals for β-anomeric forms at δ_H 5.60 and 5.63, each being a doublet with $J_{1,2}$ 8.2, these values comparing well with those of authentic sample of penta-*O*-acetyl-α,β-D-galactose. The ^{13}C NMR spectrum with signals at δ_C 89.50 and 92.02 confirmed the presence of an α,β-mixture of anomers.

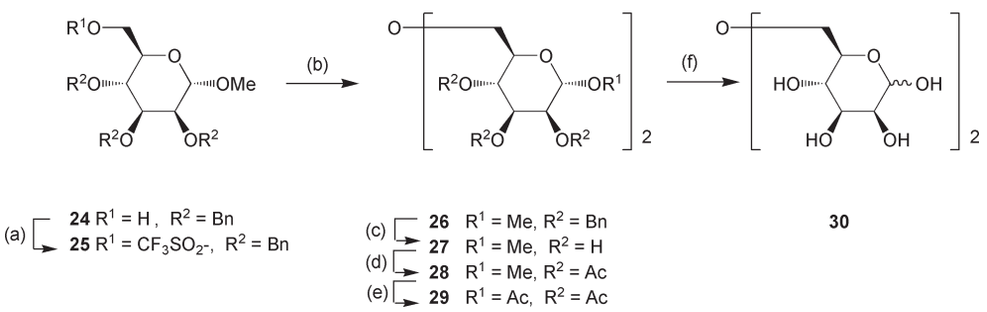
A second report of a 6,6′-ether linked disaccharide prior to present research[3,4] dates from 1961 when Whistler and Frowein[11] reported heating together equimolar amounts of 1,2-*O*-isopropylidene-α-D-glucofuranose and 5,6-anhydro-1,2-*O*-isopropylidene-α-D-glucofuranose at 150 °C, which yielded, after hydrolysis of the product and extensive purification by column chromatography, a compound they named as 6,6′-di-D-glucose anhydride. A similar method was used more recently by Villa and co-workers[12] in constructing amphiphiles based on 6,6′-ether linked D-glucose residues. Although this general approach initially seemed attractive for preparation of this type of compound, it was not followed in the present work since an attempt (not reported) to prepare the 6,6′-ether linked *allo*-derivative by fusing together 3,5-di-*O*-benzyl-1,2-*O*-isopropylidene-α-D-allofuranose and 5,6-anhydro-3-*O*-benzyl-1,2-*O*-isopropylidene-αD-allofuranose[13] was unsuccessful, the reactants showing remarkable stability even at elevated temperatures. Instead, a displacement reaction on the *gluco* 6-triflate **18**, readily prepared from the known[14] **17**, with the sodium alkoxide of **17** was made to give **19** as a crystalline solid in high yield (Scheme 4). Compound **19** showed the characteristic shift for 6-C to low field in its ^{13}C NMR spectrum compared to **17**. Catalytic hydrogenolysis of **19** gave **20**, which on acetylation gave the hexaacetate **21**. Acetolysis of the latter gave the crystalline octaacetate **22** as the α,α-isomer containing a trace (<5% from the ^1H NMR spectrum) of the β-pyranose ester, which on de-*O*-acetylation afforded the 6,6-*gluco*-ether **23** as a hygroscopic solid. Doublets in its ^1H NMR spectrum in D_2O at 5.21 ($J_{1,2}$ 3.7) and 4.63 ($J_{1,2}$ 8.6), indicated the presence of α- and β-pyranose rings and signal integration indicated an α/β ratio of 0.56, values which are very similar to those for D-glucose [δ_H 5.09 ($J_{1,2}$ 3.6) and δ_H 4.51 ($J_{1,2}$ 7.8)][10] and 0.61.[6] In the ^{13}C NMR spectrum of **23** in D_2O, 12 signals of varying intensity could be distinguished, representing the maximum number from a single molecule containing α- and β-moieties; in theory 24 signals are possible if distinguishable resonances were to arise from α,α-, β,β-, and α,β-isomers. The anomeric carbons in the α- and β-pyranose



Scheme 3 *Reagents and conditions*: (a) $Tf_2O/C_5H_5N/CH_2Cl_2$, 82%. (b) **12**, NaH/THF then **13**, 82%. (c) $CF_3CO_2H–H_2O$ (9 : 1), 97%. (d) Ac_2O/C_5H_5N, 50%.



Scheme 4 *Reagents and conditions*: (a) $Tf_2O/Et_3N/CH_2Cl_2$. (b) **17**, NaH/THF then **18**, 98%. (c) H_2/Pd–C/EtOH–EtOAc, 86%. (d) Ac_2O/C_5H_5N, 52%. (e) Ac_2O–AcOH–H_2SO_4, 73%. (f) EtONa/EtOH, 89%.



Scheme 5 *Reagents and conditions*: (a) $Tf_2O/Et_3N/CH_2Cl_2$, 82%. (b) **24**, NaH/THF then **25**, 79%. (c) H_2/Pd–C/EtOH–EtOAc, 91%. (d) Ac_2O/C_5H_5N, 97%. (e) Ac_2O–AcOH–H_2SO_4, 89%. (f) EtONa/EtOH, 95%.

rings resonate at δ_C 92.83 and 96.68, respectively, in close agreement with the values for D-glucose,[7] and importantly there is no signal below δ_C 70, confirming the 6,6′-ether link, since 6-C of α- and β-D-glucose resonate at δ_C 61.6 and 61.7, respectively.[7]

The mp (204.5–212 °C) and $[\alpha]_D$ (+125.4 in $CHCl_3$) of the α,α-octaacetate **22** differ markedly from those reported by Whistler and Frowein[11] (mp 171 °C and $[\alpha]_D$ +61 in $CHCl_3$) for the compound they term 6,6′-di-D-glucose anhydride octaacetate. This apparent anomaly is readily explained by the fact that their peracetate was prepared by treatment of their 6,6′-di-D-glucose anhydride with acetic anhydride–sodium acetate at high temperature, reaction conditions known[15] to favour formation of β-anomers. To gain evidence on this point, compound **23** was subjected to the same acetylation conditions with acetic anhydride–sodium acetate. The ^{1}H NMR spectrum of the product was fully consistent with a peracetate, and showed an α,β anomeric ratio of 0.26, indicating a preponderance of the β-anomeric acetates. The lower optical rotation reported earlier[11] compared to that of the α,α-isomer is also in accord with the presence of the β-anomer, considering the $[\alpha]_D$ values reported[15] for the α- and β-D-glucopyranose pentaacetates in $CDCl_3$ (+102 and +4, respectively).

The synthesis of the 6,6′-ether linked *manno*-isomer **30** followed a similar route to that of the *gluco*-compound. Methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside[16] **24** was converted into the triflate **25** (Scheme 5) which was then reacted with the alkoxide of **24** in THF solution to give the 6,6′-ether **26**. Removal of the benzyl groups by hydrogenolysis gave **27** which on acetylation afforded the hexaacetate **28**. Acetolysis of the latter compound gave a single stereoisomer, the α,α-octaacetate **29**, as evidenced by the signal for 1-H in its ^{1}H NMR spectrum at δ_H 6.03 ($J_{1,2}$ 1.6) and a ^{13}C NMR spectrum showing only 6 signals for ring carbons with 1-C at δ_C 90.42. Zemplén de-*O*-acetylation of **29** gave the 6,6′-*manno* ether **30**, as a hygroscopic foam. The ^{1}H NMR spectrum in D_2O of **30** contained resonances for 1-H in α- and β-pyranose moieties as broad singlets at δ_H 5.16 and 4.89, respectively, in an α,β ratio of 1.82, in agreement with the δ_H values for 1-H in D-mannose[10] in D_2O and the α,β ratio of 1.9 in aqueous solution.[6] The predominance of the α-anomeric form is confirmed in the ^{13}C NMR spectrum, in which the peak for the α-anomeric carbon at δ_C 94.82 is more intense than that for the β-anomeric carbon at δ_C 94.44, the values of these shifts agreeing well with those of D-mannose[7] in the same solvent. The shift for 6-C at δ_C 70.86 has the characteristic shift to low field compared to that at δ_C 62.1 in D-mannose.[7]

A clear comparison of the NMR spectroscopic data presented by Pérez and co-workers[2] for coyolosa with data for compounds obtained in the present research is hindered by an apparent discrepancy in the stated solvent used in the original publication[2] which reports measurement in $CDCl_3$, a solvent in which the polyhydroxy compound is unlikely to be soluble. Significantly, however, the stated ^{13}C chemical shift for 6-C at δ_C 61.1 lies within the range of values observed[7] (in D_2O) for hexopyranosides of δ_C 59.4–62.5. None of the four 6,6′-ethers prepared in this work possess a ^{13}C resonance below the value of δ_C 67.28, and it is clear from an examination of data on the compounds prepared here in cases where unequivocal comparisons are possible that the conversion of a 6-CH_2OH group into the corresponding symmetrical ether brings about a chemical shift to low field in the ^{13}C resonance of between 7.4 and 9.6 ppm. Further, all four of the 6,6′-ethers **10**, **15**, **23**, and **30** exhibit ^{13}C spectra having more than the 6 signals reported[2] for coyolosa, as a result of the non-uniform anomeric composition of these compounds. The generally hygroscopic nature of the 6,6′-ethers compared to the reported crystalline nature of coyolosa is also a significant difference.

The acetate of coyolosa is presumably a single anomeric form in view of its reported[2] crystalline nature (mp 132–134 °C) and the ring carbons resonances measured in $CDCl_3$ which were allocated[2] as 91.77 (1-C), 72.82 (2-C), 89.13 (3-C)†, 69.90 (4-C), 67.88 (5-C), and 61.54 (6-C). The lowest ^{13}C resonance in acetates **11**, **16**, **22**, and **29** were at δ_C 65.90, 66.48, 68.27 and 66.17, respectively, a clear indication of non-identity of any of these compounds with coyolosa peracetate. Considering the ^{1}H and ^{13}C NMR data together, it is clear that coyolosa is not, as reported, a 6,6′-ether linked disaccharide and it seems likely that the spectroscopic data are more in agreement with a 1,1′-linked symmetrical disaccharide, an interesting possibility in view of the hypoglycemic activity of the compound.

Conclusion

The non-identity of coyolosa with the 6,6′-ethers of the hexopyranoses prepared in this work has been demonstrated, pointing to the need for further structural studies on this natural product. Attention has been drawn, however, to this relatively unexplored type of disaccharide, which may possess interesting biological

† This allocation is clearly erroneous since this value for δ_C lies within the region in which the anomeric carbon resonances are normally found.

properties, especially in view of the report[17] that an ether-linked pseudo-disaccharide containing a 5→4 D-ribose to D-glucose ether link was a constituent of the exotoxin from *Bacillus thuringiensis*, which has inhibitory action on the *de novo* synthesis of RNA and the DNA dependent RNA polymerase. Since the synthesis[18] of the sugar fragment of this endotoxin, in 1971, relatively little work on such compounds has been performed. The potential for synthesis of novel oligosaccharides by extension of the pseudo-disaccharide chain through normal glycosidation methodology, and of eventual ring closure to form novel modified cyclodextrins is being explored.

Experimental

^{1}H NMR spectra were recorded at 300 MHz on a Varian Gemini FT spectrometer, or at 400 MHz on a Varian Unity Plus spectrometer in $CDCl_3$ unless stated otherwise, with Me_4Si as internal standard. ^{13}C NMR spectra were similarly recorded at 75 MHz on a Varian Gemini FT spectrometer. For NMR spectra in D_2O, δ_H values are referenced to Me_2CO at 2.22 ppm and δ_C values to Me_2CO at 30.89 ppm. Coupling constants (*J* values) are given in Hz. Where appropriate, signal assignments were deduced by DEPT, COSY and HSQC NMR experiments. NMR data are recorded for one ring moiety only for compounds in which the two carbohydrate rings are related by symmetry. Optical rotations were measured at ambient temperature with a Perkin-Elmer model 141 polarimeter for solutions in $CHCl_3$ unless stated otherwise and $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Low and high resolution mass spectra were recorded by the EPSRC Mass Spectrometry Service Centre at the University College of Swansea. TLC was performed on silica gel (Machery-Nagel) SIL G-25UV$_{254}$ and compounds on developed plates were detected either by viewing with a UV lamp (254 nm), or by dipping into 5% solution of sulfuric acid in ethanol followed by heating to 150 °C. Column chromatography was performed Kieselgel 60 (70–230 mm mesh, Merck). Where mixed solvents were used, the ratios given are v/v. Tetrahydrofuran (THF) was obtained anhydrous by distillation from sodium metal and benzophenone once the blue colouration due to the ketyl radical had been achieved; methanol was dried by distilling from the alkoxide (formed by reaction with activated magnesium). Sodium hydride, purchased as a 60% dispersion in mineral oil, was washed with hexane before use and the weights reported refer to the oil-free material. Organic solutions were dried over anhydrous Na_2SO_4. Reactions were maintained at −78 °C by means of a dry ice-acetone bath, and at 0 °C by means of an ice bath. Compounds **3**,[5] **12**,[9] **17**,[14] and **24**[16] were prepared by literature procedures. Triflates **7**, **13**, **18**, and **25** were used immediately without characterisation, but were homogeneous by TLC.

3-*O*-Benzyl-6-*O*-(*tert*-butyldiphenysilyl)-1,2-*O*-isopropylidene-α-D-allofuranose 4

To a solution of 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-allofuranose **3** (1.42 g, 4.6 mmol) in pyridine (10 ml) was added *tert*-butyldiphenylsilyl chloride (1.43 ml, 5.5 mmol), and after 12 h at room temperature methanol (1 ml) was added and the solution was concentrated to an oil which was partitioned between CH_2Cl_2 and water. Concentration of the organic layer afforded an oil which was purified by column chromatography eluting with CH_2Cl_2–EtOAc (49 : 1 increasing in polarity to 19 : 1) to yield as an oil the silyl ether **4** (2.36 g, 94%); $[\alpha]_D$ +39 (*c* 0.6); δ_H 1.07 (9 H, C*Me*$_3$), 1.35 and 1.57 (each 3 H and s, C*Me*$_2$), 3.72–3.82 (2 H, complex, 6a- and 6b-H), 3.93 (1 H, dd, $J_{2,3}$ 4.2, $J_{3,4}$ 8.7, 3-H), 4.05 (1 H, m, 5-H), 4.10 (1 H, dd, $J_{4,5}$ 3.9, 4-H), 4.52 (1 H, dd, $J_{1,2}$ 3.6, 2-H), 4.50 and 4.67 (each 1 H and d, J_{AB} 12, OC*H*$_2$Ph), 5.72 (1 H, d, 1-H), 7.26–7.30, 7.33–7.48, 7.62–7.72 (15 H, 3 × m, Ar-H); δ_C 19.11 (Si*C*Me$_3$), 26.51 (CMe*Me*), 26.69 (C*Me*$_3$, C*Me*Me), 64.47 (6-C), 71.88 (5-C), 72.05 (*C*H$_2$Ph), 77.52 (3-C), 77.74 (2-C), 77.88 (4-C), 104.10 (1-C), 112.95 (*C*Me$_2$), 127.81–137.55 (10 C, Ar-C); *m*/*z* (CI): 566.3 $[M + NH_4]^+$. (Found: $[M + NH_4]^+$ 566.2935. $C_{32}H_{44}NO_6Si$ requires *m*/*z* 566.2932).

3,5-Di-*O*-benzyl-6-*O*-(*tert*-butyldiphenysilyl)-1,2-*O*-isopropylidene-α-D-allofuranose 5

Silyl ether **4** (2.31 g, 4.21 mmol) was dissolved in 1,2-dimethoxyethane (15 ml) and sodium hydride (0.304 g, 12.7 mmol) was added to the stirred solution followed by benzyl bromide (1.26 ml, 10.6 mmol). After 12 h, Et_3N (1 ml) was added to the mixture and after 3 h, it was partitioned between CH_2Cl_2 and water. Column chromatography of the residue obtained on concentration of the dried organic layer, with EtOAc–hexane as eluent, gave as a syrup the benzyl ether **5** (1.83 g, 68%); $[\alpha]_D$ +37 (*c* 0.67); δ_H 1.03 (9 H, s, C*Me*$_3$), 1.34 and 1.57 (each 3 H and s, C*Me*$_2$), 3.80 (2 H, d, $J_{5,6a}$ and $J_{5,6b}$ 6.2, 6a- and 6b-H), 3.97 (1 H, ddd, $J_{4,5}$ 1.6, 5-H), 4.01 (1 H, dd, $J_{2,3}$ 4.2 and $J_{3,4}$ 8.8, 3-H), 4.28 (1 H, dd, 4-H), 4.44 and 4.61 (each 1 H and d, J_{AB} 11.6, OC*H*$_2$Ph), 4.49 (1 H, dd, $J_{1,2}$ 3.7, 2-H), 4.67 and 4.73 (each 1 H and d, J_{AB} 11.6, OC*H*$_2$Ph), 5.68 (1 H, d, 1-H), 7.18–7.42 and 7.61–7.68 (20 H, 2 × m, Ar-H); δ_C 19.03 (Si*C*Me$_3$), 26.61 (C*Me*$_3$, C*Me*Me), 26.81 (CMe*Me*), 63.79 (6-C), 71.95 and 73.90 (2 × *C*H$_2$Ph), 77.13 (3-C), 77.79 (2-C), 79.13 (4-C), 79.42 (5-C), 104.11 (1-C), 112.98 (*C*Me$_2$), 127.35–137.68 (12 C, Ar-C); *m*/*z* (CI): 656.4 $[M + NH_4]^+$. (Found: $[M + NH_4]^+$ 656.3395. $C_{39}H_{50}NO_6Si$ requires *m*/*z* 656.3402).

3,5-Di-*O*-benzyl-1,2-*O*-isopropylidene-α-D-allofuranose 6

Benzyl ether **5** (1.8 g, 2.8 mmol) was dissolved in tetrahydrofuran (2 ml) and a 1 M solution of tetrabutylammonium fluoride in tetrahydrofuran (5.64 ml) was added. After storage at ambient temperature for 12 h, the solution was concentrated and the residue subjected to column chromatography (elution with EtOAc–hexane 1 : 9 to remove *tert*-butyldiphenylsilyl fluoride, followed by EtOAc–hexane 1 : 1) to give the syrupy alcohol **6** (1.03 g, 91%); $[\alpha]_D$ +103.5 (*c* 0.32); δ_H 1.36 and 1.58 (each 3 H and s, C*Me*$_2$), 2.22 (1 H, br s, OH), 3.65 (1 H, dd, $J_{5,6a}$ 5.4, $J_{6a,6b}$ 12, 6a-H), 3.68 (1 H, dd, $J_{5,6b}$ 5.4, 6b-H), 3.88 (1 H, ddd, $J_{4,5}$ 2, 5-H), 4.04 (1 H, dd, $J_{2,3}$ 4.4, $J_{3,4}$ 8.8, 3-H), 4.22 (1 H, dd, 4-H), 4.56 and 4.75 (each 1 H and d, J_{AB} 11.6, OC*H*$_2$Ph), 4.57 (1 H, dd, $J_{1,2}$ 3.6, 2-H), 4.64 and 4.72 (each 1 H and d, J_{AB} 11.6, OC*H*$_2$Ph), 5.72 (1 H, d, 1-H); δ_C 26.49 (C*Me*Me), 26.73 (CMe*Me*), 61.87 (6-C), 72.13 and 73.39 (2 × *C*H$_2$Ph), 76.76 (3-C), 77.26 (2-C), 78.05 (5-C), 79.94 (4-C), 104.07 (1-C), 113.10 (*C*Me$_2$), 127.70–138.61 (7 C, Ar-C); *m*/*z* (CI): 418.3 $[M + NH_4]^+$. (Found: $[M + NH_4]^+$ 418.2219. $C_{39}H_{50}NO_6Si$ requires *m*/*z* 418.2224).

6-*O*-(3,5-Di-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-α-D-allofuranos-6-yl)-3,5-di-*O*-benzyl-1,2-*O*-isopropylidene-α-D-allofuranose 8

A solution of alcohol **6** (0.388 g, 0.97 mmol) in dichloromethane (4 ml) containing Et_3N (0.18 ml, 1.26 mmol) was added dropwise to a cooled (−10 °C) and stirred solution of triflic anhydride (0.2 ml, 1.19 mmol) in dichloromethane (3 ml). The solution was allowed to warm to ambient temperature and then passed rapidly through a column of silica (12 g), eluting with more dichloromethane. Evaporation of the eluate at room temperature gave the triflate **7** (0.41 g, 0.77 mmol, homogeneous by TLC) which was then dissolved in THF (5 ml). This solution was added *via* a syringe to a cooled (0 °C) and stirred solution of the sodium salt of **6**, made by addition of sodium hydride (0.3 g, 1.25 mmol) to a solution of **6** (0.24 g, 0.6 mmol) in THF. The mixture was allowed to warm to ambient temperature, and after 12 h was concentrated to dryness, and the residue was purified by column chromatography with EtOAc–hexane 1 : 4 as eluent to give ether **8** (0.426 g, 91%); $[\alpha]_D$ +85.7 (*c* 0.43); δ_H 1.33 and 1.56 (each 3 H and s, C*Me*$_2$), 3.54 (2 H, d, $J_{5,6a}$ and $J_{5,6b}$ 6, 6a- and 6b-H), 3.91 (1 H, m, 5-H), 4.00 (1 H, dd, $J_{2,3}$ 3.7, $J_{3,4}$ 8.5, 3-H), 4.19 (1 H, dd, $J_{4,5}$ 1.6, 4-H), 4.44 (1 H, dd, $J_{1,2}$ 3.3, 2-H), 4.51 and 4.68 (each 1 H and d, J_{AB} 11.8, OC*H*$_2$Ph), 4.63 (2 H, s, OC*H*$_2$Ph), 5.65 (1 H, d, 1-H), 7.17–7.38 (10 H, m, Ar-H); δ_C 26.54 and 26.84 (C*Me*$_2$), 71.41 (6-C), 72.04 and 73.52 (2 × *C*H$_2$Ph), 77.13 (3-C), 77.43 (5-C), 77.68 (2-C), 79.45 (4-C), 104.15 (1-C), 112.98 (*C*Me$_2$), 127.35–139.04 (8 C, Ar-C); *m*/*z* (CI): 800.5 $[M + NH_4]^+$. (Found: $[M + NH_4]^+$ 800.3995. $C_{46}H_{58}NO_{11}$ requires *m*/*z* 800.4004).

6-*O*-(6-Deoxy-1,2-*O*-isopropylidene-α-D-allofuranos-6-yl)-1,2-*O*-isopropylidene-α-D-allofuranose 9

A solution of ether **8** (0.29 g, 0.37 mmol) in a mixture of EtOAc–EtOH (1 : 1, 8 ml) was stirred under an atmosphere of hydrogen in the presence of 10% palladium–charcoal catalyst (73 mg) for 12 h. After filtration through kieselguhr, the filtrate was concentrated to give compound **9** as an oil (0.133 g, 85%); $[\alpha]_D$ +56.7 (*c* 1.33); δ_H 1.29 and 1.51 (each 3 H and s, C*Me*$_2$), 3.60 (1 H, dd, $J_{5,6a}$ 3.9, $J_{6a,6b}$ 10, 6a-H), 3.68 (1 H, dd, $J_{5,6b}$ 3.4, 6b-H), 3.85 (1 H, dd, $J_{3,4}$ 8.6, $J_{4,5}$ 3.5, 4-H), 4.01 (1 H, m, 5-H), 4.09 (1 H, dd, $J_{2,3}$ 4.3, 3-H), 4.58 (1 H, dd, $J_{1,2}$ 3.7, 2-H), 5.71 (1 H, d, 1-H); δ_C 26.31–26.64 (C*Me*$_2$), 68.88 (5-C), 69.94 (3-C), 71.30 (6-C), 79.75 (2-C), 81.08 (4-C), 103.42 (1-C), 112.78 (*C*Me$_2$); *m*/*z* (CI): 440.3 $[M + NH_4]^+$ (Found: $[M + NH_4]^+$ 440.2129. $C_{18}H_{34}NO_{11}$ requires *m*/*z* 440.2126).

6-*O*-(6-Deoxy-D-allos-6-yl)-D-allose 10

Compound **9** (0.122 g, 0.29 mmol) was dissolved in trifluoroacetic acid–water (9 : 1, 1 ml) and after 10 min at room temperature the solution was evaporated to dryness at <30 °C. Ether was then added to, and evaporated from the residue several times and finally a solution of the residue in water was freeze-dried to give, as a feathery, light, hygroscopic solid, ether **10** (0.095 g, 96%); $[\alpha]_D$ +19.1 (*c* 0.83, H_2O), 1-H-α/1-H-β pyranose ratio: 0.16; δ_H (D_2O) (major isomer) 3.41 (1 H, dd, $J_{1,2}$ 8.2, $J_{2,3}$ 3, 2-H), 3.61–3.76 (2 H, complex, 4- and 6a-H), 3.81 (1 H, br d, $J_{6a,6b}$ 11, 6b-H), 3.86–3.94 (1 H, complex, 5-H), 4.16 (1 H, dd, $J_{3,4}$ 3, 3-H), 4.88 (1 H, d, 1-H); (minor isomer) 5.13 (d, $J_{1,2}$ 3.4, 1-H); δ_C (D_2O) 67.55 (4-C), 71.30 (6-C), 71.81 (2-C or 3-C), 71.86 (3-C or 2-C), 73.10 (5-C), 93.57 (minor anomer 1-C-α), 94.19 (major anomer 1-C-β); *m*/*z* (ES): 365.2 $[M + Na]^+$. (Found: $[M + Na]^+$ 365.1059. $C_{12}H_{22}O_{11}Na$ requires *m*/*z* 365.1054).

6-*O*-(1,2,3,4-Tetra-*O*-acetyl-6-deoxy-β-D-allos-6-yl)-1,2,3,4-tetra-*O*-acetyl-6-deoxy-β-D-allose 11

Acetylation of **10** (0.051 g, 0.15 mmol) with acetic anhydride–pyridine gave, after chromatography with EtOAc–hexane (1 : 1) the octaacetate **11** (0.063 g, 62%) which afforded the crystalline product from EtOAc–hexane; mp 198–199 °C; $[\alpha]_D$ −4 (*c* 0.45); δ_H 2.00, 2.01, 2.11, 2.15, (each 3 H and s, C*H*$_3$CO), 3.56 (1 H, dd, $J_{5,6a}$ 4.8, $J_{6a,6b}$ 11.8, 6a-H), 3.67 (1 H, dd, $J_{5,6b}$ 3, 6b-H), 4.10 (1 H, ddd, $J_{4,5}$ 8.4, 5-H), 4.97 (1 H, dd, $J_{1,2}$ 8.7, $J_{2,3}$ 3, 2-H), 4.98 (1 H, dd, $J_{3,4}$ 3, 4-H), 5.70 (1 H, dd, 3-H), 5.97 (1 H, d, 1-H); δ_C 20.38 (× 2), 20.52, 20.76 (*C*H$_3$CO), 65.90 (2- or 4-C), 68.03 (4- or 2-C), 68.28 (3-C), 70.22 12 (6-C), 72.90 (5-C), 90.06 (1-C), 169.09, 169.13, 169.95, 169.34 (4 × -*C*O-); *m*/*z* (CI): 696.3 $[M + NH_4]^+$. (Found: $[M + NH_4]^+$ 696.2348. $C_{28}H_{42}NO_{19}$ requires *m*/*z* 696.2346).

6-*O*-(6-Deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranos-6-yl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose 14

A solution of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose **12** (1.3 g, 5 mmol) in CH_2Cl_2 containing pyridine (0.40 ml, 5 mmol) was added dropwise to a stirred and cooled (0 °C) solution of triflic anhydride (1 ml, 6.1 mmol) in CH_2Cl_2, the resulting solution allowed to reach room temperature, and then extracted rapidly with ice–water. The organic layer was dried, concentrated and the crude triflate **13** (1.61 g, 4.1 mmol) was dissolved in THF (6 ml). This solution was added to a cooled (0 °C) solution of the sodium alkoxide of **12** prepared by reacting, under nitrogen, a solution of **12** (1.09 g, 4.2 mmol) in THF (10 ml) with NaH (0.21 g, 8.6 mmol). The stirred mixture was allowed to reach ambient temperature and, after 48 h, EtOH (0.5 ml) was added and solvent was then removed under reduced pressure. The residue was distributed between CH_2Cl_2 and water and the organic layer dried and concentrated to yield material which TLC (EtOAc–hexane 1 : 4, 3 developments) showed to contain some starting alcohol **12** and a predominant amount of a faster moving component. Column chromatography (EtOAc–hexane 1 : 2) gave the ether **14** (1.0 g, 82% based on reacted **12**) and then recovered alcohol **12** (0.47 g). The initially syrupy **14** solidified on storage; mp 105–106 °C; $[\alpha]_D$ −85.4 (*c* 1.48); δ_H 1.31, 1.32, 1.43 and 1.52 (each 3 H and s, 2 × C*Me*$_2$), 3.63 (1 H, dd, $J_{5,6a}$ 6.8, $J_{6a,6b}$ 10.2, 6a-H), 3.73 (1 H, dd, $J_{5,6b}$ 6.2, 6b-H), 3.98 (1 H, ddd, $J_{4,5}$ 2, 5-H), 4.26 (1 H, dd, $J_{3,4}$ 8, 4-H), 4.29 (1 H, dd, $J_{1,2}$ 4.8, $J_{2,3}$ 2.4, 2-H), 4.58 (1 H, dd, 3-H), 5.51 (1 H, d, 1-H); δ_C 24.32, 24.86, 25.88 and 25.98 (2 × C(*Me*)$_2$), 66.48 (5-C), 69.81 (6-C), 70.60 (2-C), 70.63 (4-C), 71.01 (3-C), 96.34 (1-C), 108.56 and 109.19 (2 × *C*Me$_2$); *m*/*z* (CI): 520.4 $[M + NH_4]^+$. (Found: $[M + NH_4]^+$. 520.2755. $C_{24}H_{42}NO_{11}$ requires *m*/*z* 520.2758).

6-*O*-(6-Deoxy-α,β-D-galactopyranos-6-yl)-α,β-D-galactopyranose 15

Ether **14** (0.12 g) was dissolved in trifluoroacetic acid–water (9 : 1, 2 ml) and solvent was removed after 2 h at <40 °C. The residue was triturated with a mixture of MeOH–EtOAc (1 : 1, 5 ml) giving the 6,6′-ether **15** as colourless solid (0.08 g, 97%), which on heating softened to a glass at ~97 °C; $[\alpha]_D$ +55 (*c* 0.35, H_2O, 24 h), 1-H-α/1-H-β isomer ratio: 0.59, α-isomer; δ_H (D_2O) 3.68–3.89 (4 H, complex, 2-, 3-, 6a-, and 6b-H), 3.97 (1 H, d, $J_{3,4}$ 3.2, $J_{4,5}$ <1, 4-H), 4.22 (1 H, dd, $J_{5,6a}$ and $J_{5,6b}$ 5.9, 5-H), 5.25 (1 H, $J_{1,2}$ 3.7, 1-H); β-isomer, δ_H 3.48 (1 H, dd, $J_{1,2}$ 7.8, $J_{2,3}$ 10, 2-H), 3.66 (1 H, dd, $J_{3,4}$ 3.4, 3-H), 3.68–3.89 (3 H, complex, 5-, 6a-, 6b-H), 3.91 (1 H, d, $J_{4,5}$ <1, 4-H), 4.57 (1 H, d, 1-H); α-isomer, δ_C (D_2O) 68.98 (2-C), 69.36 (5-C), 69.74 (3-C), 70.19 (4-C), 71.14 and 71.41 (6-C, α,α and α,β), 93.05 (1-C); β-isomer δ_C 69.66 (4-C), 71.29 (6-C), 72.49 (2-C), 73.38 (3-C), 74.06 (5-C), 97.14 (1-C); *m*/*z* (ES): 360.1 $[M + NH_4]^+$. (Found: $[M + NH_4]^+$ 360.1504. $C_{12}H_{26}NO_{11}$ requires *m*/*z* 360.1500).

6-*O*-(1,2,3,4-Tetra-*O*-acetyl-6-deoxy-α,β-D-galactopyranos-6-yl)-1,2,3,4-tetra-*O*-acetyl-α,β-D-galactopyranose 16

Acetylation of **15** (0.21 g, 0.6 mmol) with acetic anhydride–pyridine yielded a product which was purified by chromatography (EtOAc–hexane, 1 : 1) to yield as a foam and a mixture of isomers octaacetate **16** (0.20 g, 50%); $[\alpha]_D$ +46.6 (*c* 0.41), 1-H-α/1-H-β isomer ratio: 0.83; δ_H 1.92, 1.93, 1.94, 1.95, 1.97, 2.04(7), 2.05(2), 2.06(8), 2.07, 2.08, 2.09, 2.10, 2.11 (C*H*$_3$CO), α-isomer‡, 3.30–3.60 (2 H, complex, 6a- and 6b-H), 4.15 and 4.27 (1 H, both dd, $J_{5,6a}$ and $J_{5,6b}$ 6.1, 5-H), 5.18–5.28 (2 H, complex, 2- and 3-H), 5.38 and 5.40 (1 H, each br s, 4-H), 6.27 (1 H, br s, 1-H); β-isomer, δ_H 3.30–3.60 (2 H, complex, 6a- and 6b-H), 3.87 and 3.90 (1 H, each dd, $J_{5,6a}$ and $J_{5,6b}$ 6, 5-H), 5.00 and 5.01 (1 H, each dd, $J_{2,3}$ 10, $J_{3,4}$ 3.3, 3-H), 5.18–5.28 (1 H, complex, 2-H), 5.31 and 5.33 (1 H, each d, 4-H), 5.60 and 5.63 (1 H, each d, $J_{1,2}$ 8.2, 1-H); δ_C 20.39, 20.45, 20.50, 20.64, 20.78 (*C*H$_3$CO), 66.48, 67.10, 67.27, 67.31, 67.74, 67.82, 67.88, 69.13, 69.39, 69.48, 69.66, 69.78, 70.03, 70.68, 70.74, 72.79, 72.98, 89.50 (1-C-α), 92.02 (1-C-β), 168.91, 169.04, 169.32, 169.72, 169.81, 169.89 (-*C*O-); *m*/*z* (CI): 696.4 $[M + NH_4]^+$. (Found: $[M + NH_4]^+$ 696.2353. $C_{28}H_{42}NO_{19}$ requires *m*/*z* 696.2346).

Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(methyl 2,3,4-tri-*O*-benzyl-6-deoxy-α-D-glucopyranos-6-yl)-α-D-glucopyranoside 19

Compound **17** (0.68 g, 1.46 mmol) was dissolved in CH_2Cl_2 (5 ml) containing Et_3N (0.33 ml, 2.38 mmol) and the solution was added dropwise to a stirred, cooled (−10 °C) solution of triflic anhydride (0.39 ml, 2.38 mmol) in CH_2Cl_2 (4 ml). The reaction mixture was allowed to warm to room temperature, partially concentrated, and the solution added to a chromatographic column (25 g of silica) which was then eluted CH_2Cl_2. Concentration of the eluate gave the crude triflate **18**, which was dissolved in THF (5 ml) and added to a cooled (0 °C) and stirred solution of the alkoxide of **17** (under nitrogen) prepared by adding NaH (0.058 g, 2.43 mmol) to alcohol **17** (0.54 g, 1.16 mmol) dissolved in THF (4 ml). The coolant was removed, and after stirring for a further 12 h, the solution was concentrated and the residue distributed between CH_2Cl_2 and water. The dried organic layer showed by TLC (EtOAc–hexane, 1 : 1)

‡ In some cases, two signals can arise from a hydrogen at one position in an α- or β-anomeric form of one pyranose ring, depending on the anomeric configuration in the attached pyranose ring.

no alcohol at R_f 0.33 and a new component with R_f 0.55. Column chromatography of the crude product gave the syrupy 6,6′-ether **19** (1.03 g, 98% based on **17**), which crystallised on standing to a solid; mp 84–86 °C; $[\alpha]_D$ +34.7 (*c* 1.67); δ_H 3.36 (3 H, s, OMe), 3.51 (1 H, dd, $J_{1,2}$ 3.4, $J_{2,3}$ 9.3, 2-H), 3.59 (1 H, dd, $J_{3,4}$ 9.3, $J_{4,5}$ 9.3, 4-H), 3.66 (1 H, br d, $J_{5,6a}$ <1, $J_{6a,6b}$ 10.8, 6a-H), 3.74 (1 H, dd, $J_{5,6b}$ 4.2, 5-H), 3.80 (1 H, dd, 6b-H), 4.00 (1 H, dd, 3-H), 4.58 (1 H, d, 1-H), 4.64 and 4.78 (each 1 H, d, J_{AB} 12.3, OCH_2Ph), 4.67 and 4.89 (each 1 H, d, J_{AB} 10.8, OCH_2Ph), 4.84 and 4.99 (each 1 H, d, J_{AB} 10.8, OCH_2Ph); δ_C 54.96 (OMe), 70.35 (5-C an 6-C), 73.30 (O*C*H$_2$Ph), 74.89 (O*C*H$_2$Ph), 75.72 (O*C*H$_2$Ph), 77.71 (4-C), 80.02 (2-C), 82.01 (3-C), 97.93 (1-C), 127.61–138.85 (18 C, Ar-C); *m*/*z* (ES): 928.5. $[M + NH_4]^+$. (Found: $[M + NH_4]^+$ 928.4638. $C_{56}H_{66}NO_{11}$ requires *m*/*z* 928.4630).

Methyl 6-*O*-(methyl-6-deoxy-α-D-glucopyranos-6-yl)-α-D-glucopyranoside 20

A solution of the 6,6′-ether **19** (0.62 g, 0.68 mmol) in EtOAc–EtOH (1 : 9, 20 ml) was stirred under hydrogen in the presence of 10% palladium–charcoal catalyst (0.1 g). After 24 h, TLC (EtOAc–MeOH) indicated formation of a component, R_f 0.5 with loss of **19**. After filtration through Celite® the solution was concentrated to give material (0.23 g) which was subjected to chromatography using EtOAc–MeOH (1 : 1) as eluent on silica pre-washed with the same solvent, to give, initially as an oil, compound **20** (0.22 g, 86%), which crystallised on standing to a solid; mp 81.5–87.5 °C; $[\alpha]_D$ +130.6 (*c* 0.12, H_2O); δ_H (D_2O) 3.26 (3H, s, OMe), 3.28 (1 H, dd, $J_{3,4}$ 9, $J_{4,5}$ 9, 4-H), 3.41 (1 H, dd, $J_{1,2}$ 3.6, $J_{2,3}$ 9.9, 2-H), 3.51 (1 H, dd, *J*, 3-H), 3.58–3.70 (3 H, complex, 5-, 6a-, 6b-H), 4.64 (1 H, d, 1-H); δ_C (D_2O) 55.92 (OMe), 70.92 (4-C), 71.15 (6-C), 71.80 (5-C), 72.58 (2-C), 74.38 (3-C), 100.61 (1-C); *m*/*z* (ES): 388.2 $[M + NH_4]^+$. (Found: $[M + NH_4]^+$ 388.1812. $C_{14}H_{30}NO_{11}$ requires *m*/*z* 388.1813).

Methyl 2,3,4-tri-*O*-acetyl-6-*O*-(methyl 2,3,4-tri-*O*-acetyl-6-deoxy-α-D-glucopyranos-6-yl)-α-D-glucopyranoside 21

Acetylation of the alcohol **20** (0.099 g, 0.27 mmol) with acetic anhydride (0.2 ml, 2.1 mmol) in pyridine (2 ml) afforded the product containing (TLC in EtOAc–hexane, 2 : 1) a very minor impurity, which was removed by chromatography in the same solvent system to give the syrupy hexaacetate **21** (0.087 g, 52%); $[\alpha]_D$ +152.1 (*c* 0.87); δ_H 1.97, 1.99 and 2.03 (each H, and s, MeCO), 3.37 (3 H, s, OMe), 3.48–3.62 (2 H, complex, 6a- and 6b-H), 3.88 (1 H, ddd, $J_{4,5}$ 10.2, $J_{5,6a}$ 4, $J_{5,6b}$ 4, 5-H), 4.84 (1 H, dd, $J_{1,2}$ 3.3, $J_{2,3}$ 9.9, 2-H), 4.90 (1 H, d, 1-H), 4.99 (1 H, dd, $J_{3,4}$ 9.6, 4-H), 5.43 (1 H, dd, 3-H); δ_C 20.48 (× 2) and 20.84 (*C*H$_3$CO), 55.14 (OMe), 68.66 (5-C), 69.00 (4-C), 70.09 (3-C), 70.49 (6-C), 70.82 (2-C), 96.48 (1-C), 169.71, 170.22 and 170.27 (3 × -*C*O-); *m*/*z* (ES): 640.2 $[M + NH_4]^+$. (Found: $[M + NH_4]^+$ 640.2446. $C_{26}H_{42}NO_{17}$ requires *m*/*z* 640.2447).

1,2,3,4-Tetra-*O*-acetyl-6-*O*-(1,2,3,4-tetra-*O*-acetyl-6-deoxy-α-D-glucopyranos-6-yl)-α-D-glucopyranose 22

The hexaacetate **21** (0.123 g, 0.2 mmol) was dissolved in an acetolysis mixture of acetic anhydride–acetic acid–sulfuric acid (35 : 15 : 1 v/v/v, 1 ml) and after 12 h the mixture was diluted with CH_2Cl_2 and the organic solution was washed with sat. aq. $NaHCO_3$, water and dried. Concentration gave the product **22**, initially as a syrup (0.098 g, 73%), which afforded crystals on trituration with EtOH; mp 204.5–212 °C; $[\alpha]_D$ +125.4 (*c* 0.36), δ_H 1.99, 2.01. 2.03 and 2.15 (each 3H and s, MeCO), 3.53 (1 H, dd, $J_{5,6a}$ 3.4, $J_{6a,6b}$ 11.7, 6a-H), 3.58 (1 H, dd, $J_{5,6b}$ 3.4, 6b-H), 3.99 (1 H, ddd, $J_{4,5}$ 9.8, 5-H), 5.06 (1 H, dd, $J_{1,2}$ 3.6, $J_{2,3}$ 9.8, 2-H), 5.14 (1 H, dd, $J_{3,4}$ 9.8, 4-H), 5.44 (1 H, dd, 3-H), 5.65 (<5% of 1-H-α, d, $J_{1,2}$ 8.1, 1-H-β), 6.28 (1 H, d, 1-H-α); δ_C 20.30, 20.45, 20.57, and 20.73 (*C*H$_3$CO), 68.27 (4-C), 69.24 (2-C), 69.85 (3-C), 70.13 (6-C), 71.47 (5-C), 88.99 (1-C), 169.05, 169.51, 169.82 and 170.46 (4 × -*C*O-); *m*/*z* (CI): 696.3 $[M + NH_4]^+$. (Found: $[M + NH_4]^+$ 696.2344. $C_{28}H_{42}NO_{19}$ requires *m*/*z* 696.2346).

6-*O*-(6-Deoxy-α,β-D-glucopyranos-6-yl)-α,β-D-glucopyranose 23

To a solution of the octaacetate **22** (0.139, 0.22 mmol) in dry ethanol (3 ml) was added small amount (~2 mg) of sodium to produce a catalytic amount of sodium ethoxide to bring about deacylation. A precipitate formed which was collected after 12 h and dried over P_2O_5 to afford a light brown product (0.068 g, 89%). A portion (0.052 g) was eluted from a small column of silica with EtOAc–MeOH (1 : 1) to give the sample for optical rotation and NMR spectroscopy of the 6,6′-ether **23** (0.029 g) as a hygroscopic solid; $[\alpha]_D$ +46.2 (*c* 0.29, H_2O), 1-H-α/1-H-β isomer ratio: 0.56, α-isomer; δ_H (D_2O) 3.38–3.88 (6 H, complex, 2-, 3-, 4-, 6a-, and 6b-H), 3.94 (1 H, ddd, $J_{4,5}$ 9.9, $J_{5,6a}$ and $J_{5,6b}$ 3.6, 5-H), 5.21 (1 H, d, $J_{1,2}$ 3.7, 1-H); β-isomer, δ_H 3.24 (1 H, dd, $J_{1,2}$ and $J_{2,3}$ 8.6, 2-H), 3.47 (1 H, dd, $J_{3,4}$ 9, 3-H), 3.38–3.88 (4 H, complex, 4-, 5-, 6a-, and 6b-H), 4.63 (1 H, d, 1-H); δ_C (D_2O) 70.32, 70.41, 70.71, 70.83, 70.96, 72.12, 73.42, 74.76 (2-C-β), 75.40, 76.40, 92.83 (1-C-α), 96.68 (β-1-C); *m*/*z* (ES): 360.1 $[M + NH_4]^+$. (Found: $[M + NH_4]^+$ 360.1496. $C_{12}H_{26}NO_{11}$ requires *m*/*z* 360.1500).

Acetylation 23 with acetic anhydride–sodium acetate

Using the conditions reported by Whistler and Frowein,[11] compound **23** (0.011 g) was treated with acetic anhydride (0.8 ml) and sodium acetate (0.04 g) at an elevated temperature (oil bath, 150 °C). Isolation of the product by pouring into ice–water followed by extraction with CH_2Cl_2 gave a homogeneous, syrupy product (R_f 0.4 in EtOAc–hexane) (0.018 g, 83%); 1-H-α/1-H-β isomer ratio: 0.26, α-isomer; δ_H 5.46 (dd, $J_{2,3}$ and $J_{3,4}$ 9.9, 3-H), 6.31 (d, $J_{1,2}$ 3.8, 1-H); β-isomer, δ_H 5.24 and 5.25 (each dd, $J_{2,3}$ and $J_{3,4}$ 9.4, 3-H), 5.67 and 5.70 (each d, $J_{1,2}$ 8.2, 1-H) (only clearly resolved resonances are reported in each case).

Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(methyl 2,3,4-tri-*O*-benzyl-6-deoxy-α-D-mannopyranos-6-yl)-α-D-mannopyranoside 26

A solution of methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside **24** (1 g, 2.15 mmol) in CH_2Cl_2 (7 ml) containing Et_3N (0.37 ml, 2.64 mmol) was added dropwise to a stirred, cooled (−10 °C) solution of triflic anhydride (0.43 ml, 2.62 mmol) in CH_2Cl_2 (6 ml). The temperature of the mixture was allowed to rise to ambient temperature and TLC (CH_2Cl_2) showed complete conversion to a new product (R_f 0.7). The solution was absorbed onto a column of silica which was then eluted with CH_2Cl_2 and combination and evaporation of the relevant fractions gave the triflate **25** (1.05 g, 1.76 mmol). The triflate was dissolved in THF (6 ml) and added slowly under nitrogen to a cool (0 °C) solution of the alkoxide of **24**, prepared by adding NaH (0.083 g, 3.5 mmol) to alcohol **24**(0.8 g, 1.72 mmol) dissolved in THF (6 ml). The coolant was removed, the mixture stirred for 12 h, and the residue remaining after evaporation of solvent from the mixture was distributed between CH_2Cl_2 and water. The separated organic layer was dried and concentrated to a syrup (1.33 g) which on TLC showed a new component (R_f 0.4) with only a trace of starting alcohol (R_f 0.1). Column chromatography, eluting initially with EtOAc–hexane (2 : 5) gave as a syrup the 6,6′-ether **26** (0.95 g, 79% based on utilised alcohol, 0.19 g of **24** being obtained by further elution); $[\alpha]_D$ +31.1 (*c* 0.36); δ_H 3.25 (3 H, s, OMe), 3.72–3.84 (4 H, complex, 2-, 5-, 6a-, and 6b-H), 3.87 (1 H, dd, $J_{2,3}$ 2.9, $J_{3,4}$ 9.3, 3-H), 3.93 (1 H, dd, $J_{4,5}$ 9.3, 4-H), 4.62 (2 H, s, OCH_2Ph), 4.66 and 4.71 (each 1 H, d, $J_{A,B}$ 12.8, OCH_2Ph), 4.67 and 4.91 (each 1 H, d, $J_{A,B}$ 10.8, OCH_2Ph), 4.69 (1 H, d, $J_{1,2}$ 1.8, 1-H), 7.15–7.4 (15 H, complex, Ar-H); δ_C 54.49 (OMe), 70.95 (6-C), 71.86 (5-C), 72.07 (O*C*H$_2$Ph), 72.56 (O*C*H$_2$Ph), 74.63 (2-C), 75.01 (O*C*H$_2$Ph), 75.10 (4-C), 80.21 (3-C), 98.75 (1-C), 127.43–138.68 (11 C, Ar-C); *m*/*z* (CI): 928.6 $[M + NH_4]^+$. (Found: $[M + NH_4]^+$ 928.4631. $C_{56}H_{66}NO_{11}$ requires *m*/*z* 928.4630).

Methyl 6-*O*-(methyl 6-deoxy-α-D-mannopyranos-6-yl)-α-D-mannopyranoside 27

A solution of the 6,6′-ether **26** (0.89 g, 0.98 mmol) in EtOAc–EtOH (3 : 13, 20 ml) was stirred under hydrogen in the presence of 10%

palladium–charcoal catalyst (0.1 g). After 18 h TLC (EtOAc–hexane, 1 : 1) showed reaction was not complete and acetic acid (0.1 ml) was added. After a further 30 h some starting material remained and a further amount of EtOH (3 ml) and acetic acid (0.1 ml) was added and stirring continued for a further 24 h, after which time starting material was no longer apparent by TLC. The filtered solution was concentrated and the residue chromatographed with EtOAc–MeOH (3 : 1) as eluent on a silica column pre-washed in the same solvent to give a solid foam the title compound **27** (0.33 g, 91%); softens ~80 °C; $[\alpha]_D$ +95.5 (*c* 0.18, MeOH); δ_H (D_2O) 3.40 (3 H, s, OMe), 3.67 (1 H, dd, $J_{3,4}$ 9.5, $J_{4,5}$ 9.5, 4-H), 3.74 (1 H, ddd, $J_{5,6b}$ 1.6, 5-H), 3.75 (1 H, dd, $J_{2,3}$ 3.2, 3-H), 3.79 (1 H, dd, $J_{5,6a}$ 5.9, $J_{6a,6b}$ 10.7, 6a-H), 3.87 (1 H, br d, 6b-H), 3.93 (1 H, dd, $J_{1,2}$ 1.4, 2-H), 4.74 (1H, d, 1-H); δ_C (D_2O) 55.49 (OMe), 67.50 (4-C), 70.54 (2-C), 70.93 (6-C), 71.20 (3-C), 72.05 (5-C), 101.67 (1-C); *m*/*z* (ES): 371.2 $[M + H]^+$. (Found: $[M + H]^+$ 371.1547. $C_{14}H_{27}O_{11}$ requires *m*/*z* 371.1548).

Methyl 2,3,4-tri-*O*-acetyl-6-*O*-(methyl 2,3,4-tri-*O*-acetyl-6-deoxy-α-D-mannopyranos-6-yl)-α-D-mannopyranoside 28

Compound **27** (0.3 g, 0.81 mmol) was acetylated by treatment with acetic anhydride (0.6 ml, 6.4 mmol) in pyridine (5 ml) to give as a hard glass the hexaacetate **28** (0.49 g, 97%); $[\alpha]_D$ +53.8 (*c* 0.92); δ_H (400 MHz) 1.92, 1.97 and 2.07 (each 3 H and s, MeCO), 3.33 (3H, s, OMe), 3.50 (1 H, dd, $J_{5,6a}$ 6.3, $J_{6a,6b}$ 10.6, 6a-H), 3.54 (1 H, dd, $J_{5,6b}$ 3, 6b-H), 3.88 (1 H, ddd, $J_{4,5}$ 10.1, 5-H), 4.62 (1 H, d, $J_{1,2}$ 1.6, 1-H), 5.09 (1 H, dd, $J_{3,4}$ 10.1, 4-H), 5.15 (1 H, dd, $J_{2,3}$ 3.3, 2-H), 5.26 (1 H, dd, 3-H); δ_C 20.5, 20.6, and 20.7 (3 × *C*H_3CO-), 54.92 (OMe), 66.72 (4-C), 68.96 (3-C), 69.45 (2-C), 69.72 (5-C), 71.03 (6-C), 98.23 (1-C), 169.98 (× 2), 170.12, (3 × -*C*O-); *m*/*z* (CI): 640.3 $[M + NH_4]^+$. (Found: $[M + NH_4]^+$ 640.2443. $C_{26}H_{42}NO_{17}$ requires *m*/*z* 640.2447).

1,2,3,4-Tetra-*O*-acetyl-6-*O*-(1,2,3,4-tetra-*O*-acetyl-6-deoxy-α-D-mannopyranos-6-yl)-α-D-mannopyranose 29

The hexaacetate **28** (0.4 g, 0.64 mmol) was dissolved in an acetolysis mixture of acetic anhydride–acetic acid–sulfuric acid (35 : 15 : 1 v/v/v, 3 ml) and after 12 h the mixture was diluted with CH_2Cl_2 (100 ml) and the organic solution was washed with sat. aq. $NaHCO_3$, water and then dried. TLC (EtOAc–hexane, 1 : 1, 3 developments) indicated a pure compound R_f 0.6. Evaporation of the solvent afforded the octaacetate **29** (0.39, 89%) as a foam; $[\alpha]_D$ +58.2 (*c* 0.18); δ_H 1.99 (3 H), 2.07 (3 H), and 2.15 (6 H) (each s, MeCO), 3.48 (1 H, dd, $J_{5,6a}$ 6.2, $J_{6a,6b}$ 11.2, 6a-H), 3.63 (1 H, dd, $J_{5,6b}$ 2.7, 6b-H), 3.98 (1 H, ddd, $J_{4,5}$ 10, 5-H), 5.21 (1 H, dd, $J_{3,4}$ 10, 4-H), 5.22 (1 H, dd, $J_{1,2}$ 1.6, $J_{2,3}$ 3.4, 2-H), 6.03 (1 H, dd, 3-H), 6.03 (1 H, d, 1-H); δ_C 20.52, 20.57, 20.62, and 20.73 (4 × *C*H_3CO), 66.17 (4-C), 68.30 (2-C), 68.68 (3-C), 70.97 (6-C), 72.11 (5-C), 90.42 (1-C), 168.35, 169.88, 169.94, and 170.12 (4 × -*C*O-); *m*/*z* (ES): 696.3 $[M + NH_4]^+$. (Found: $[M + NH_4]^+$ 696.2343. $C_{28}H_{42}NO_{19}$ requires *m*/*z* 696.2346).

6-*O*-(6-Deoxy-α-D-mannopyranos-6-yl)-α-D-mannopyranose 30

Sodium (~1 mg) was added to a solution of octaacetate **29** (0.33 g, 0.49 mmol) in dry ethanol and after 12 h a chip of solid CO_2 was added and the solvent removed by evaporation. The solid residue was repeatedly extracted with portions of a solvent mixture of EtOAc–MeOH (1 : 1) and the extracts combined and concentrated to yield as a hygroscopic foam the title compound **30** (0.158 g, 95%); $[\alpha]_D$ +18.0 (*c* 0.66, H_2O), 1-H-α/1-H-β isomer ratio: 1.82, α-isomer; δ_H (D_2O) 3.67 (1 H, dd, $J_{3,4}$ and $J_{4,5}$ 10.6, 4-H), 3.73–3.98 (complex, 2-, 3-, 5-, 6a- and 6b-H), 5.16 (1 H, br s, 1-H); β-isomer; δ_H 3.50 (1 H, br ddd, 5-H), 3.59 (1 H, dd, $J_{3,4}$ and $J_{4,5}$ 9.6, 4-H), 3.73–3.98 (complex, 2-, 3-, 6a- and 6b-H), 4.89 (1 H, br s, 1-H); α-isomer, δ_C (D_2O) 67.58 (4-C), 70.86 (3-C and 6-C), 71.34 (2-C), 71.75 (5-C), 94.82 (1-C); β-isomer, δ_C 67.28 (4-C), 70.86 (6-C), 71.88 (2-C), 73.67 (3-C), 75.52 (5-C), 94.44 (1-C); *m*/*z* (ES): 365.1 $[M + Na]^+$. (Found: $[M + Na]^+$ 365.1066. $C_{12}H_{22}O_{11}Na$ requires *m*/*z* 365.1054).

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